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Highlights

- CFR decline may not imply that vaccines are being effective in reducing deaths
- A constant CFR can still mean that vaccines are effective in reducing deaths
- Detecting infections among both the vaccinated and unvaccinated population is key
- Unless vaccinated people are tested, the CFR loses meaning in tracking the pandemic

The impact of COVID-19 vaccines on the Case Fatality Rate: The importance of monitoring breakthrough infections

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Abstract

Objectives

Test the behavior of the case fatality rate in a mixed population of vaccinated and unvaccinated individuals by illustrating the role of both the effectiveness of

vaccines in preventing deaths and the detection of infections among both the vaccinated (breakthrough infections) and unvaccinated individuals.

Methods

We simulate three hypothetical case fatality rate scenarios that result from a different combination of vaccine effectiveness in preventing deaths and the efforts in detecting infections among both the vaccinated and unvaccinated individuals.

Results

In the presence of vaccines, the case fatality rate depends not only on the effectiveness of vaccines in preventing deaths, but also on the detection of breakthrough infections. As a result, a decline in the case fatality rate may not imply that vaccines are being effective in reducing deaths. Likewise, a constant case fatality rate can still mean that vaccines are effective in reducing deaths.

Conclusions

Unless vaccinated people are also tested, the case fatality rate loses its meaning in tracking the pandemic. This shows that unless efforts are directed at detecting breakthrough infections, it is hard to disentangle the effect of vaccines in reducing deaths from the probability of detecting infections on the case fatality rate.

Key-words: COVID-19; Vaccine effectiveness; Case-Fatality Rate; Breakthrough Infections

Main Text

Introduction

With an increasing testing capacity, vaccination is supposed to necessarily lead to a decline in the CFR, since vaccinated individuals may still get infected but develop less severe symptoms than non-vaccinated individuals (Hall et al. 2021). Indeed, if the same testing strategy is maintained before and after vaccines are introduced, a declining CFR would imply that vaccines are preventing deaths. However, we show that the CFR depends not only on the effectiveness of vaccines in reducing deaths among the vaccinated, but also on detecting infections among both vaccinated and unvaccinated individuals. Thus, the CFR can either increase, decrease or remain constant, even if the infection fatality rate of the vaccinated is lower than the infection fatality rate of the unvaccinated. This feature highlights the importance of detecting infections among vaccinated individuals, or the so-called breakthrough infections. A vaccine breakthrough infection is defined as the detection of SARS-CoV-2 RNA or antigen in a respiratory specimen collected from a person ≥14 days after all recommended doses of a U.S. Food and Drug Administration (FDA) authorized COVID-19 vaccine (NNDSS 2021). As of May 1, 2021, the Centers for Disease Control and Prevention (CDC) stopped monitoring all reported vaccine breakthrough cases to focus on identifying and investigating only symptomatic breakthrough cases that lead to hospitalization or death (Centers for Disease Control and Prevention 2021), despite rising cases in breakthrough infections (Hacisuleyman et al.

2021). According to the CDC, the reason for focusing on breakthrough cases that lead to hospitalization or death is to “maximize the quality of the data collected on cases of greatest clinical and public health importance” (Centers for Disease Control and Prevention 2021). The CDC maintained that ongoing support would be provided to state health departments to identify SARS-CoV-2 infections among vaccinated individuals and register them at the National Notifiable Diseases Surveillance System (NNDSS), but the focus has been on health-care workers and local clusters (Britton 2021; Keehner et al. 2021).

Understandably, the rationale for focusing on lethal outcomes and hospitalizations stems mainly from the burden of severe symptomatic SARS-CoV-2 on health infrastructure, which pushed health systems to the limit globally (Lal et al. 2021). However, studying all breakthrough infections is not only critical for monitoring real-world vaccine effectiveness against variants and whether they are outsmarting vaccines (Cyranoski 2021; Mina and Andersen 2021; Lipsitch et al. 2021), but it is also key for accurately measuring vaccine effectiveness in reducing deaths. We illustrate the latter point by showing how the case fatality rate (CFR) in the presence of vaccines depends both on the effectiveness of vaccines in preventing deaths among the infected *and* on the ratio of the detection rates between the vaccinated and the unvaccinated.

By illustrating how the case fatality rate (CFR) is sensitive to both the effectiveness of vaccines in preventing deaths among the infected and the ratio

of the detection rates between the vaccinated and the unvaccinated, we derive two important results. First, we show the effect of undetected positive cases among vaccinated individuals and consequently the impact of not tracking all breakthrough infections. Second, we illustrate the behavior of the CFR in a mixed population of vaccinated and unvaccinated individuals. This is a contribution to the discussion on how policy makers and other stakeholders should be aware of these effects when using or interpreting these values, as the CFR has already been shown to be dependent on demographic factors, delays and timing in reported cases, and consistent testing policies (Dowd et al. 2020; Goldstein and Lee 2020; Dudel et al. 2020; Harman et al. 2021).

Our results suggest that it is thus crucial to maintain testing efforts in order to detect cases both among vaccinated and unvaccinated individuals, even if those infections do not evolve to severe cases or death (The Rockefeller University 2021; Mina and Andersen 2021; Lipsitch et al. 2021). Failing to properly keep track of all cases, irrespective of vaccination status, leads to the same scenario of the beginning of the pandemic, on which governments and researchers were only able to detect a part of the infections, missing key information from asymptomatic transmission, as testing was restricted to severe and hospitalized cases (Li 2020; Nishiura 2020; Wu et al. 2020). This in turn leads to an imprecise knowledge of the current spread of the virus among the vaccinated and the unvaccinated population, which consequently leads to distorted estimates of vaccine effectiveness at the population level. This also prevents us from

accurately identifying what are the sociodemographic factors associated to breakthrough infections and their long-term consequences on health.

Background

It has been widely acknowledged that the CFR is an indicator that is sensitive to demographic factors, delays in reported cases, and testing policies. (Dowd et al. 2020; Rajgor et al. 2020; Goldstein and Lee 2020; Green et al. 2020; Harman et al. 2021; Smith 2021; Luo et al. 2021; Undurraga et al. 2021). The CFR is defined as the ratio between the number of confirmed deaths from a disease and the number of reported cases in a given time. Hence, any factor that impacts these numbers will affect the CFR (Rajgor et al. 2020; Green et al. 2020). Of particular importance is the ability of detecting cases via testing. Since testing availability may be limited and testing strategies may change over time, not every case is reported. This leads to an artificially high CFR, overestimating the risk of death. On the other hand, vital registration systems may experience delays in reporting deaths or face underreporting issues. In that case, the CFR can be artificially low, underestimating the risk. Hence, because these variations in the CFR may not reflect the true mortality risk, its interpretation requires caution and awareness.

In the presence of vaccines, there is an added complexity to the CFR, as it will also depend on the detection of infections among vaccinated individuals and on

the effectiveness of vaccines in preventing deaths. With increased testing capacity, vaccination is supposed to lead to a decline in the CFR, since vaccinated individuals may still get infected but develop less severe symptoms than non-vaccinated individuals (Hall et al. 2021). Nonetheless, that is not what happens necessarily in the observed CFR, at least not for several months after vaccination uptake, as shown in Fig 1. Israel was the first country to have strong vaccine uptake with the country fully vaccinating half of its total population in just two months after the rollout began (December 19, 2021). This trend was overturned by Malta, that despite a slower pace in the beginning of the vaccination rollout (24 Jan, 2021), had already 80% of its total population fully vaccinated by August 2021. The US started a few days before Israel but had a slower initial reaction and reached higher levels only by the end of 2021 (~60%). Austria increased its vaccination pace starting June 2021 and by September of the same year had slightly more than 60% of its population fully vaccinated. For the majority of the countries selected, the trajectories of the percentage vaccinated follow a similar S-shaped curve, with a sharper increase in the beginning followed by some months of stability. Brazil is an exception with a slower initial uptake that lasted almost 6 months followed by an almost linear increase from August 2021-December 2021. However, despite the country-specific differences in the timing and pace of vaccination, the respective CFRs remained relatively stable through most of the observed time period (see Figure 1).

[Fig 1 Here]

Fig 1. Left part of the graph refers to year 2020, previous to vaccination and with the %Case-Fatality Rate (CFR) in selected countries (From April 2020 to mid-Dec 2021). The right part of the graph includes the share of fully vaccinated persons (%), with the * dashed line starting with the first vaccine uptake country (United States, Dec 13, 2020, followed, in order, by: Israel= Dec. 19, 2020; United Kingdom= Dec. 20, 2020, Austria= Dec. 27, 2020; Italy=Dec. 27, 2020; Brazil= Jan. 16, 2021; Malta= 24 Jan, 2021. We end in mid-December to consider most cases before Omicron becomes the majority of the cases. Before February 2021, most countries had not started to massively vaccinate as well as were amidst the 2020 winter lockdowns, so we consider the vaccination trajectory after February. Source: Our World in Data (Mathieu et al. 2021).

This may lead to a questioning of whether vaccines are not being effective in reducing deaths in most of these countries. For instance, are we supposed to interpret that the CFR starting to decline in the United Kingdom after July means that vaccines are being more effective there while in Malta and Israel they are not? In order to shed light into what is driving those patterns we look into how the CFR behaves in the presence of vaccines for a specific age group.

Methods

In the presence of vaccines, additional factors affect the CFR, since we have a mixed population of vaccinated and unvaccinated individuals. Considering a population that is not yet 100% vaccinated – which is the case for the majority of global populations currently -, we can define the total CFR as the weighted sum of the CFR of the unvaccinated ($CFR_{t,a}^{U}$) and the CFR of the vaccinated ($CFR_{t,a}^{V}$):

$$\mathrm{CF}R_{t,a} = \mathrm{CF}R_{t,a}^{U}\left(1-\gamma_{t,a}\right) + \mathrm{CF}R_{t,a}^{V}\,\gamma_{t,a}, \#(1)$$

where the weight $\gamma_{t,a}$ is the ratio between the total number of vaccine breakthroughs and the total number of ever infected and detected cases (see appendix for a full derivation of $\gamma_{t,a}$). Previous work showed that the CFR of the unvaccinated can be expressed as the ratio of the fatality rate at age a among the unvaccinated (m_a) to the probability of detecting persons ever infected until time t at age a among the unvaccinated ($d_{t,a}^{U}$) (Sánchez-Romero et al. 2021). The CFR of the vaccinated can be expressed in the same manner, with the difference that the fatality rate pertains to deaths among the vaccinated while the detected refers to infections among the vaccinated. If we consider that the probability of dying for the vaccinated is $\beta_a \in (0,1)$ times lower than for the unvaccinated, we can express the fatality rate of the vaccinated as $m_a(1-\beta_a)$. Hence, the CFR in the presence of vaccines is:

$$\mathrm{CF}R_{t,a} = \frac{m_a}{d_{t,a}^{U}}\left(1-\gamma_{t,a}\right) + \frac{m_a(1-\beta_a)}{d_{t,a}^{V}}\gamma_{t,a} = \frac{m_a}{d_{t,a}^{U}}\left(\left(1-\gamma_{t,a}\right) + \frac{(1-\beta_a)}{Z_{t,a}}\gamma_{t,a}\right) \#(2)$$

with $Z_{t,a} = d_{t,a}^{V}/d_{t,a}^{U}$, being the ratio of the probability of detecting cases among vaccinated to detecting cases among unvaccinated. This result shows that the CFR depends not only on how effective vaccines are in preventing deaths $(1 - \beta_a)$ (refer to the Supplementary Material for an extension on vaccine effectiveness definition considering prevention of transmission), but also on the probability of detecting both infected persons among the vaccinated $d_{t,a}^{V}$ - breakthrough infections -, and infected persons among the unvaccinated $d_{t,a}^{U}$. This relationship indicates that the lower (resp. higher) the effectiveness of vaccination preventing deaths (i.e. a higher value of $1 - \beta_a$), the more (resp. less) we have to detect among the vaccinated (i.e. a higher value of $Z_{t,a}$), in order to keep the CFR constant. In other words, a scenario of constant CFR can indicate a low (resp. highly) effective vaccine with high (resp. limited) detection among the vaccinated compared to the unvaccinated. Ideally, the best scenario is a high vaccine effectiveness coupled with a high detection rate among vaccinated individuals.

To illustrate the sensitivity of the CFR to the interaction between vaccine effectiveness in preventing deaths and the efforts in detecting infections among both the vaccinated and unvaccinated individuals, we simulate three hypothetical CFR scenarios that result from a different combination of β_a and $Z_{t,a}$ values. In order to better illustrate the sensitivity of the CFR, we will focus on the oldest age group, that has the highest risk of dying and was the first vaccinated. By using

the oldest-age group, we avoid the potential bias produced by the different vaccination strategies by age. Because age-specific data on deaths, vaccination rates and testing are not harmonized across countries, we will illustrate with the case of Austria, for which we have detailed data on deaths, infections, vaccination status and testing by age (See data on Supp. Material for more details). In addition, not only is Austria the second country in the world with the highest level of testing as of August 15 (Hasell et al. 2020), but it also has mandatory molecular PCR-RT testing for in-person services, entering bars and restaurants, as well as engaging in some in-door activities like gym and public pools. The observed CFR is calculated using data from BMSGPK, Österreichisches COVID-19 Open Data Informationsportal (2021), while the simulated CFR values are calculated using data from (Richter et al. 2020a, b). Following Hall et al. (2021) the value of vaccine effectiveness in reducing deaths for ages above 84 is set at 0.85 (Hall et al. 2021). The initial simulated CFR value is assumed to be equal to the average CFR value observed between February and November, 2021. For details on the simulation and key relationships between vaccine effectiveness, detection rates and the CFR we refer the reader to the Supplementary Material. Total CFR for selected countries and their share of fully vaccinated persons are from Our World in Data (Mathieu et al. 2021). In addition, all data, codes and methods used in this paper are provided by the authors in https://osf.io/uvwdj/?view_only=517e735ca10848adacd73b93a40eb9c0.

Results

We will illustrate with the case of Austria, with a focus on the oldest age group (84+), that has the highest risk of dying and was the first vaccinated. By end of December 2021, a little over 90% of persons above age 84 were fully vaccinated, as shown in panel (B), in Fig. 2. Nonetheless, similar to several countries depicted in Fig. 1, the CFR for the age group 84+ in Austria also remained stable across time (Fig 2., panel A). If the detection rate of the unvaccinated does not change over time, the observed constant CFR occurs because the effort in detecting the infected among the vaccinated relative to the unvaccinated $Z_{t,84+}$ is equal to effectiveness of vaccination in preventing deaths $1 - \beta_{84+}$.

[Fig 2 Here]

Fig 2. Panel (A) %Case-Fatality Rate (CFR); Panel (B) Share of fully vaccinated persons (%). Austria, by age, from Jan to Dec 2021. Source: The number of people vaccinated at each group is taken from BMSGPK, Österreichisches COVID-19 Open Data Informationsportal (2021)

To illustrate this point, we simulate three hypothetical CFR scenarios that result from a different combination of vaccine effectiveness in reducing deaths, which we call β_a, and the detection rate of infections among vaccinated compared to unvaccinated persons which we call $Z_{t,a}$ - or to what extent are governments willing to detect both breakthrough infections and infections among unvaccinated

persons (For a full derivation of the CFR in the presence of vaccines and the parameters used for the simulation we refer the reader to the Supp. Material). First, Fig 3 presents how different combinations of β_{84+} and $Z_{t,84+}$ values can yield constant CFRs, going from the lowest value of vaccine effectiveness to the highest (Panels A-C, respectively). The dark red solid line in each panel is the observed CFR for the age group 84+ from January 2021 to December 2021 and the black lines are estimated CFR trajectories conditional on β_{84+} and $Z_{t,84+}$ values. Noteworthy of mention, Fig 3 is a zoomed-in version of the panel A in Fig 2. While the %CFR in panel A in Fig 2 ranges from 0% to 23%, in Fig 3 it varies between 21% and 23%. After a whole year with vaccines, it is very difficult to say that there is a clear decline in the CFR from February to November 2021 with the %CFR varying from 21% and 23%. Panel A shows that the CFR remains constant when the detection of breakthrough infections relative to non-vaccinated individuals is high ($Z_{t,84+} = 0.75$), despite low vaccine effectiveness. Conversely, when the effectiveness of vaccines in reducing deaths is high, and thus a decline in the CFR should necessarily be observed, the CFR can remain constant when the ability of detecting infections among the vaccinated is low (Panel C, for $Z_{t,84+} = 0.25$). Second, when the efforts of detecting the infected among the vaccinated, relative to the unvaccinated ($Z_{t,84+}$), is lower than the ability of vaccines in preventing deaths $(1 - \beta_{84+})$, the CFR will increase.

[Fig 3 Here]

Figure 3. Evolution of the %CFR for the age group 84+ in Austria (Jan-Dec 2021) by three different parameter values of β_{84+} and $Z_{t,84+}$. Source: Observed CFR calculated using data from BMSGPK, (2021). Simulated CFR values are calculated using data from (Richter et al. 2020b, a)and BMSGPK, COVID-19 Open Data Informationsportal (2021). Note: The initial value of the simulated CFR is assumed to be equal to the average CFR value observed between February and November, 2021. For more details, refer to the Supplementary Material.

This latter scenario may happen, for instance, in a context where governments only track breakthrough infections among those who present severe symptoms (which leads to a high CFR among the vaccinated). Does that mean that vaccines are not being effective in reducing deaths among Austrians aged 84+? Not necessarily, since the CFR also depends on testing policies and the capacity of countries in detecting both breakthrough infections and infections among unvaccinated individuals. This shows that unless efforts are directed at detecting infections among vaccinated (i.e., all breakthrough cases) and unvaccinated individuals, it is hard to disentangle the effect of vaccines in reducing deaths from the probability of detecting infections on the CFR.

Discussion

The fact that the CFR is an indicator that is sensitive to demographic factors, case reporting and testing strategies has been widely acknowledged in the

literature. This had led specialists to argue that the CFR needs to be interpreted with caution, since it may not accurately reflect the true mortality risk. Our contribution to this debate is to additionally demonstrate how the CFR behaves in the presence of vaccines. We show that the CFR also depends on whether breakthrough cases are being accurately detected. Thus, in the absence of information on infections among both the vaccinated and the unvaccinated, the CFR may be misleading, especially when used to assess the effectiveness of vaccines in reducing deaths or the spread of the virus. A declining CFR like that observed in the UK starting July 2021could either indicate that the virus is reducing its mortality rate or alternatively that young unvaccinated individuals are infected at higher rates than vaccinated older age groups. With no knowledge on the positivity rate among the vaccinated and unvaccinated it becomes very difficult to disentangle those factors. We observe for most countries that despite a high proportion of vaccinated individuals, the CFR does not significantly decline for almost a year after vaccine uptake. That was even more remarkable for cases like Austria, that has an exceptional consistent testing strategy throughout time. This reinforces that widespread testing is still a key policy strategy in order to detect asymptomatic or mild infections among both the vaccinated and unvaccinated population (The Rockefeller University 2021). Efforts to properly detect those cases are important for assessing immunity duration (Seow et al. 2020) and if extra booster shots will be needed, especially with new more contagious variant spreading quickly throughout the world and more breakthrough infections recorded (Kupferschmidt 2021; Barda et al. 2021; Arbel

et al. 2021; Andrews et al. 2022; Watson 2022). This may be a decisive factor in informing governments on the different set of strategies they may need to employ throughout the pandemic, including a mixture of vaccines and non-pharmaceutical measures (Dagan et al. 2021) , as immunity to SARS-CoV-2 infection may progressively wane with time (Haghpanah et al. 2021; Reynolds 2021; Stamatatos 2021) and the availability or logistics of subsequent phases of mass vaccination may not take place as fast as needed or for all age groups simultaneously.

On a further note, while most people who develop COVID-19 and survive are able to recover within weeks or a few months, depending on the level of disease severity, a part of those individuals suffers from chronic damage to their lungs, heart, kidneys or brain, while others will develop long COVID – a different subset of chronic illnesses and extreme lingering effect (Carfì et al. 2020; NIH 2021; Vaes et al. 2021). If we do not keep track of the characteristics of vaccinated individuals who have mild breakthrough infections, we not only hamper a proper estimation of vaccine failure rates based on age, gender, ethnicity, medication use, or immune function, but also miss important information on factors that aggravate long covid symptoms.

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Conflict of Interest

The Authors declare no competing interests.

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Ethical Approval statement

This study does not perform analysis in human subjects and/or animals. All data used are publicly available and noted in the main text and supplementary materials. Additionally, the authors provide the codes and data to replicate the study at https://osf.io/uvwdj/?view_only=517e735ca10848adacd73b93a40eb9c0.

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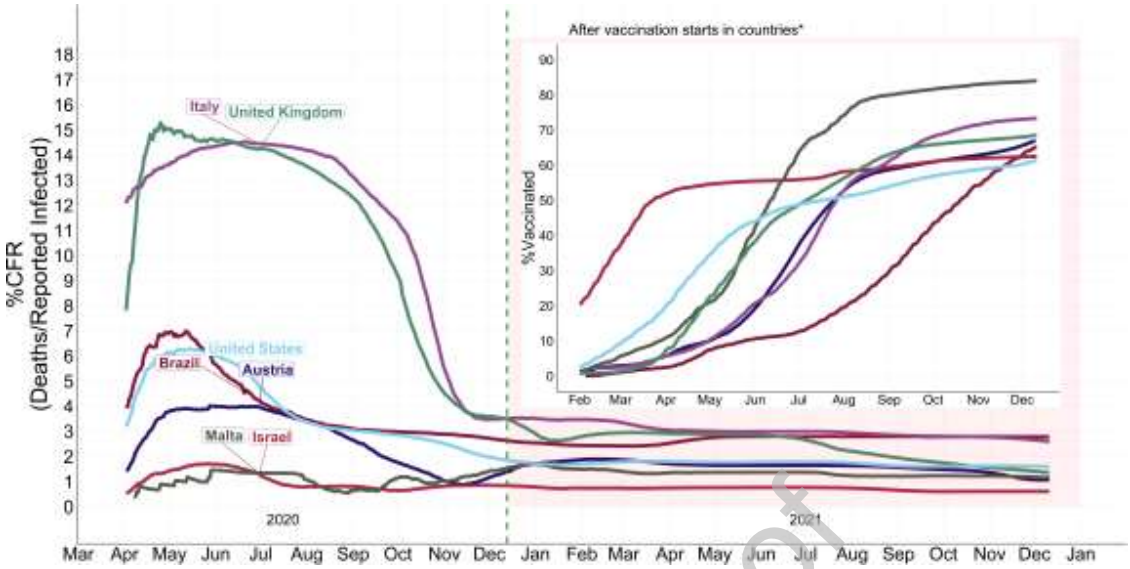

Fig. 1

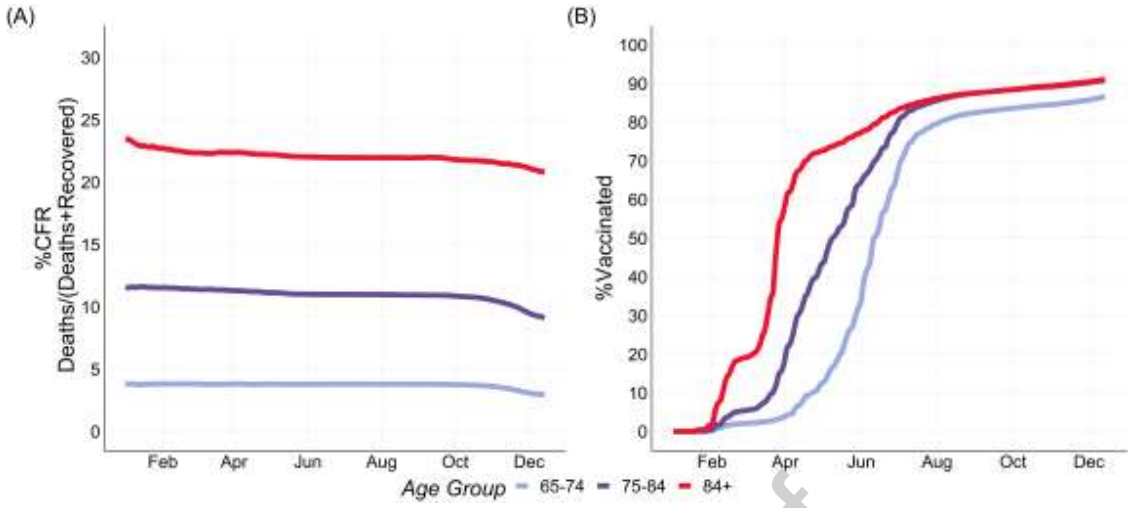

Fig. 2

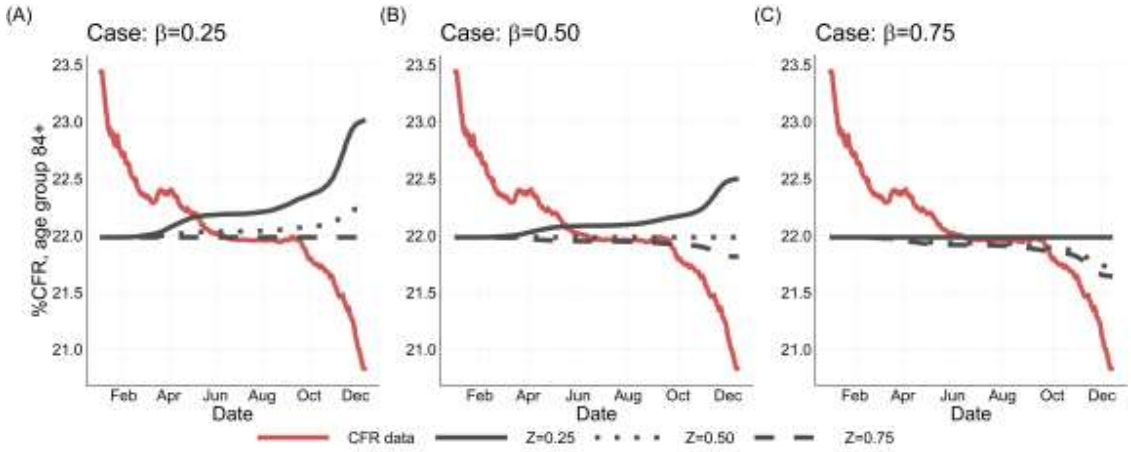

Fig. 3